

**THE INVENTION CLAIMED IS:**

1. A method for manipulating the intrinsic strain of cells, comprising treating the cells either *in vivo* or *in vitro* with compounds that affect the intrinsic strain setpoint of the cells in order to modulate extracellular matrix synthesis, secretion, stiffness, organization and/or remodeling, or attachment of the cells to the matrix via integrins or other like cell-matrix attachments.

2. The method according to claim 1, wherein the cells comprise an *in situ* native tissue.

3. The method according to claim 1, wherein the cells comprise an *in vitro* fabricated tissue engineered construct.

4. The method according to claim 3, wherein the tissue engineered construct is a human tendon internal fibroblast (HTIF)-populated bioartificial tendon (BAT<sup>TM</sup>) or other fibroblast from another connective tissue.

5. The method according to claim 3, wherein the compound is added at the beginning, during or at the end of fabrication of the tissue engineered construct.

6. The method according to claim 1, further comprising applying a mechanical external strain to the cells.

7. The method according to claim 6, wherein the mechanical external strain is comprised of uniaxially loading a tissue engineered construct by placing Arctangle<sup>TM</sup> loading posts beneath a well of a culture plate and applying a vacuum to deform a flexible membrane downward so as to apply a uniaxial strain along a long axis of the tissue engineered construct.

8. The method according to claim 1, wherein the compound is a mediator which causes release of cell attachment points of the cells from its extracellular matrix.

9. The method according to claim 8, wherein the mediator is selected from the group consisting of binding site peptides, such as collagen, elastin, fibronectin or laminin-binding site peptides; decorin; biglycan; fibromodulin; and lumican.

10. The method according to claim 1, wherein the compound is a ligand that modulates attachment and tensional structuring of the cells to the extracellular matrix so as to cause a relaxation of the cells.

11. The method according to claim 10, wherein the ligand is selected from the group consisting of adenosine triphosphate, adenosine diphosphate, adenosine monophosphate, uridine triphosphate, uridine diphosphate, uridine monophosphate and uridine triphosphate.

12. The method according to claim 1, wherein the compound, such as hyaluronic acid, reduces extracellular matrix remodeling.

13. The method according to claim 1, wherein the compound is a cytokine which adjusts the intrinsic strain of cells by modulating gene expression, said gene expression selected from the group consisting of cytoskeletal genes that express cytoskeletal proteins selected from the group consisting of actin, myosin,  $\alpha$ -actinin, vimentin, vinculin, titin and others; genes that express elastin; and genes that express matrix metalloproteinases.

14. The method according to claim 13, wherein the cytokine is selected from the group consisting of interleukin-1beta (IL-1 $\beta$ ) and tumor necrosis factor-alpha (TGF- $\alpha$ ).

15. The method according to claim 1, wherein the compound interferes with actin polymerization to decrease the modulus of the cells and thus decrease its intrinsic strain, said compound selected from the group consisting of cytochalasin D, cytochalasin B and colchicines.

16. The method according to claim 1, wherein the compound, such as nocodazole, disrupts the microtubular network and thus increases cell modulus.

17. The method according to claim 1, wherein the compound is an interfering RNA compound to cytoskeletal genes that express cytoskeletal proteins, said cytoskeletal proteins selected from the group consisting of actin, myosin,  $\alpha$ -actinin, vimentin, vinculin and titin, matrix metalloproteinase genes and other genes that regulate the intrinsic strain setpoint of the cells.

18. The method according to claim 17, wherein the interfering RNA compound is introduced into tissue engineered constructs *in vitro* or into native tissue *in situ*.